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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,857	11/15/2001	Avi J. Ashkenazi	P2730P1C43	7807

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 03/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

HL

Office Action Summary	Application No.	Applicant(s)	
	09/997,857	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/8/04*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-123* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment filed 08 December 2004 has been entered in full. Claims 1-118 and 124 were cancelled. Claims 119-123 are under examination.

The Declaration of Avi Ashkenazi under 37 CFR1.132, filed 08 December 2004, has been entered.

The Declaration of Paul Polakis under 37 CFR1.132, filed 08 December 2004, has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

The information disclosure statement(s) (IDS) filed 08 December 2004 was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

Withdrawn Objections And/Or Rejections

The rejection to claims 119-124 under 35 U.S.C. 112, second paragraph, as set forth at page 7 of the previous Office Action (24 June 2004), is *withdrawn* in view of the amendment (08 December 2004).

Priority

The priority of the instant application is denied because the priority does not meet the requirements of 35 USC 112, First Paragraph. Therefore, the effective filing date for the purposes of applying art is the same as the actual filing date, 15 November 2001. The basis for this is forth at page 7 of the previous Office Action (24 June 2004).

Applicant states that they rely on the gene amplification assay for patentable utility in this case, which was first disclosed in International Application PCT/US00/03565, filed 11 February 2000. Applicant maintains that they are entitled to an effective date of 11 February 2000.

It is suggested that Applicant submit a copy of the referenced gene amplification assay from International Application PCT/US00/03565 to receive a filing date of 11 February 2000 for the instant application.

Claim Rejections - 35 USC § 101

Claims 119-123 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. The basis for this rejection is set forth at pages 2-6 of the previous Office Action (24 June 2004).

Applicant cites the Utility Examination Guidelines 66 Fed. Reg. 1092 (2001), MPEP 2107 II (B) and the Revised Interim Utility Guidelines Training Materials, 1999. Applicant submits that gene amplification is an essential mechanism for oncogene activation and the assay is well described in Example 170 of the present amplification.

Applicant argues that PRO1185 showed a 2.0139-fold to 3.317 fold amplification in lung or colon tumors, which is significant and thus the PRO1185 gene has utility as a diagnostic marker.

Applicant criticizes the Examiner's reliance on Haynes *et al.,* Pennica *et al.* and Konopka *et al.* (all of record). Applicant states that Haynes *et al.* teach that there was a general trend but no strong correlation between protein expression and transcript levels. Applicant states that the teachings of Pennica *et al.* are specific for WISP family genes and are not directed to genes in general. Applicant argues that Konopka does not disclose any generalized teaching about the correlation between protein expression and gene amplification and the reference is not sufficient to establish a *prima facie* showing of lack of utility based on the results of the abl gene alone. Applicant asserts that the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. Applicant discusses the references (Orntoft *et al.,* Hyman *et al.* and Pollack *et al.*) submitted in the IDS to demonstrate that if a gene is amplified in cancer, it is more than likely than not that the encoded protein will be expressed at an elevated level.

Applicant's arguments have been fully considered but are not deemed persuasive. Orntoft *et al.* appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and protein levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft *et al.* do not appear to look at gene amplification, mRNA levels and protein levels from a single gene at a time. The instant specification reports data

regarding amplification of individual genes, which may or may not be in a chromosomal region which is highly amplified. Orntoft *et al.* concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO1185 in the instant specification. That is, it is not clear whether or not PRO1185 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance of Orntoft *et al.* is not clear. Hyman *et al.* used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract). Protein levels were not investigated. Therefore, Hyman *et al.* also do not support utility of the claimed proteins. Pollack *et al.* also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack *et al.* did not investigate protein levels. Therefore, Pollack *et al.* also do not support the asserted utility of the claimed invention. The three papers state that the research was relevant to the development of **potential** cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specification's assertions that the claimed PRO1185 have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

The Examiner is questioning whether the asserted utility is specific or substantial. No evidence has been submitted that it is the norm rather than the exception that protein levels are increased when gene amplification occurs in cancer. The state of the art regarding gene amplification and increased protein levels can be opposing as indicated by the references cited by the Examiner and Applicant. Indeed, given the

disclosure in art, such as Pennica *et al.,* Konopka *et al.,* and Haynes *et al.,* that there is not always such a correlation, the skilled artisan would not assume it is so, **but would perform the experiment to verify it** (Emphasis added). Therefore, the art indicates that it is not the norm that gene amplification, or even increased transcription, results in increased protein levels. Given how small the DNA copy number of PRO1185 increased, and the evidence provided by Haynes *et al.,* Pennica *et al.* and Konopka *et al.,* it was clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA or protein levels. Such further research requirements makes it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete.

Applicant directs the Examiner's attention to the Declaration by Dr. Polakis. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Dr. Polakis argues that in approximately 80% of their observations, they have found that increases in the level of a particular mRNA level correlates with changes in the level of protein expressed from that mRNA when human tumor cells are compared

with their corresponding normal cells. Dr. Polakis contends that it is central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.

The Declaration of Paul Polakis under 37 CFR 1.132 filed 08 December 2004 is insufficient to overcome the rejection of claims 119-123 based upon 35 U.S.C. 101 as set forth in the last Office action. Applicant's arguments have been fully considered but are not found persuasive because **there is no indication in the specification or in the declarations that the PRO1185 mRNA or protein levels increase or stay the same** (Emphasis added). The instant specification provides no information regarding increased mRNA levels of PRO1185 in tumor samples relevant to normal samples. Only gene amplification data was presented. The Polakis declaration is limited to a discussion of data regarding the correlation of mRNA levels and protein levels, and not gene amplification levels and protein levels. Furthermore, the declaration does not provide data such that the Examiner can independently draw conclusions, since only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu *et al.* (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray

(p. 408, middle of right column). Hu *et al.* discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). Further research would be needed to determine PRO1185 mRNA and protein levels in cancers showing gene amplification of PRO1185 gene. The proposed use of the PRO1185 proteins as claimed in this application are simply starting points for further research and investigation into potential practical uses of the proteins and antibodies.

Applicant directs the Examiner's attention to the Declaration by Dr. Ashkenazi. Applicant argues that a polypeptide encoded by a gene that is amplified in squamous cell carcinomas of lung would still have a credible, specific and substantial utility. Dr. Ashkenazi states that if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. Dr. Ashkenazi argues that if a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product. Applicant discusses Hanna *et al.* (reference submitted in the IDS). Applicant argues that the reference teaches that the HER-2/neu gene has been shown to be amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40%-

60% of intraductal breast carcinoma. Applicant submits that the reference teaches that the diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as over expression of the HER-2/neu gene product (by IHC). Applicant contends that even when the protein is not over-expressed, the assay relying on both test leads to a more accurate classification of the cancer and a more effective treatment of it.

The Declaration of Avi Ashkenazi under 37 CFR 1.132 filed 07 December 2004 is insufficient to overcome the rejection of claims 119-123 based upon 35 U.S.C. 101 as set forth in the last Office action. Dr. Ashkenazi discussion regarding various scenarios of how increased copy number of a gene can have utility in the absence of over-expression of the corresponding gene product is not found persuasive because a significant difference in the cancer samples relative to normal tissue was not detected for the claimed invention. Applicant's discussion of Hanna *et al.* is not found persuasive. Hanna *et al.* teach that HER-2/neu is an oncogene that encodes a transmembrane glycoprotein. Studies have indicated that high levels of expression of the protein are associated with rapid tumor growth. The gene has been shown to be amplified and/or overexpressed in invasive breast cancer and intraductal breast carcinoma. HER-2/neu oncogene has been identified as having value regarding treatment regimen and prognosis. Such is not the case for the instant invention. The instant specification fails to teach a correlation between the instant invention and treatment regimens and/or prognosis for lung or colon tumors. The instant specification fail to teach tumors size or whether the deltaCt data was corrected for aneuploidy. A slight amplification of a gene

does not necessarily mean that the gene is overexpressed in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid, as amplification of proto-oncogenes and aneuploidy is commonly observed in human tumors. Aneuploidy can also occur in damaged/abnormal, but not in cancerous cells, for example Down's syndrome cells. Thus the mechanism by which gene amplification occurs is very important. Most importantly, Hanna *et al.* teach that subsets of tumors are found which show discordant results such as protein overexpression without gene amplification or lack of protein overexpression with gene amplification. **Hanna *et al.* teach that the clinical significance of such results is unclear and based on the above considerations, HER-2/neu testing will ultimately utilize immunohistochemistry as a screen, followed by FISH in IHC-negative cases.** The instant specification fails to show any sort of correlation between gene amplification and high level expression of the protein.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 USC § 112, First paragraph, Enablement

Claims 119-123 remain rejected under 35 U.S.C. 112, first paragraph, enablement. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed

invention. The basis for this rejection is set forth at pages 6-7 of the previous Office Action (24 June 2004).

Applicant incorporates their response to the rejection under 35 USC 101 in response to the rejection under 35 USC 112, first paragraph. Applicants arguments have been fully considered but are not found to persuasive for the reasons discussed above in the maintained rejection in 35 USC 101.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 USC § 102(e)

Claims 119-123 remain rejected under 35 U.S.C. 102(e) as being anticipated by LaFleur *et al.,* US Patent No. 6,569,992 B1. The basis for this rejection is set forth at pages 7-8 of the previous Office Action (24 June 2004).

Applicant argues that LaFleur discloses a protein sequence that has 87% protein identity to polypeptide SEQ ID NO:401 (PRO1185). Applicants submit that claim 124 has been canceled and claim 119 has been amended to recite that the instantly claimed antibodies "specifically bind" to the polypeptide of SEQ ID NO:401. Applicant maintains that antibodies that would bind to the LaFleur polypeptide are not encompassed in these claims.

Applicant's arguments have been fully considered but are not deemed persuasive because there are long stretches of amino acids that are 100% identical to SEQ ID NO:401. It appears that these stretches cover a good portion of the

extracellular domain (amino acids 1-158). Please see sequence search Appendix A (submitted by the Examiner in the previous Office Action, 24 June 2004). Thus an antibody made against the protein of LaFleur could specifically bind a polypeptide comprising SEQ ID NO:401.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RMD
2/28/05

Elizabeth C. Kemmerer